CASE REPORTS

Hemorrhagic Ascites: An Unusual Complication Of Multiple Myeloma

JAMES L. POTH, M.D., AND
RALPH P. GEORGE, M.D., *Stanford*

POSTMORTEM RECOGNITION of extra-medullary tumor involvement in patients with multiple myeloma is not uncommon[1-5] but the occurrence of hemorrhagic ascites in human myeloma is distinctly unusual. In the case here reported recurrent hemorrhagic ascites developed 22 months after the diagnosis of multiple myeloma was made.

Report of a Case

The patient, a 45-year-old Caucasian woman, was in good health until early 1968, at which time she was found to be pancytopenic. On physical examination in March 1968 no abnormality was noted. Leukocytes numbered 2,200 per cu mm, with 46 percent granulocytes, 51 percent lymphocytes and 3 percent monocytes. The hematocrit was 24 percent, hemoglobin 8.0 grams per 100 ml, reticulocyte count 1.2 percent and platelet count 98,000 per cu mm. Bone marrow biopsy revealed patchy infiltration with plasma cells, many of which were immature. However, myelopoiesis and erythropoiesis appeared normal. A direct Coombs' test was positive to a titer of 1:4. Serum protein electrophoresis demonstrated a gamma globulin spike of 5.4 gm per 100 ml. Immunoelectrophoretic analysis revealed the presence of an IgG myeloma protein, type K. Electrophoresis of concentrated urine revealed no abnormal protein. Serum calcium, blood urea nitrogen (BUN), serum creatinine, partial thromboplastin time (PTT), prothrombin time (PT), and bleeding time were all within normal limits. A radiographic skeletal survey revealed no abnormalities.

Following transfusion with two units of packed red blood cells, therapy was initiated with cyclophosphamide, 100 mg a day, and prednisone, 40 mg a day. The subsequent course is depicted in Chart 1. After two weeks of prednisone therapy the Coombs' test was negative.

In November 1969, because of a gradual rise in the myeloma protein and increasing neutropenia in the face of a bone marrow examination demonstrating reduction of myeloid elements and patchy infiltration of immature plasma cells, cyclophosphamide was discontinued. Intermittent four-day therapy with melphalan, 0.25 mg per kg of body weight per day, and prednisone, 2.0 mg per kg per day, was begun 23 November 1969. Six weeks after completion of the second course of this therapy, the patient noted progressive abdominal swelling over a one-week period. On examination elsewhere on 23 February 1970 the

From the Division of Hematology, Stanford University School of Medicine.

Submitted October 5, 1970.

Reprint requests to: Department of Medicine (Hematology), Stanford University School of Medicine, Stanford, Ca. 94305 (Dr. J. L. Poth).

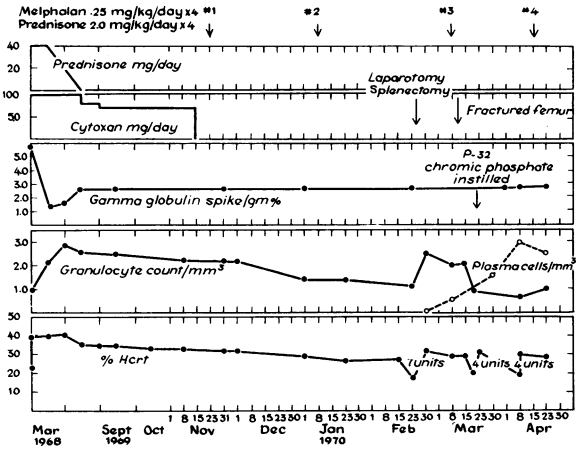

Chart 1.—Course of patient in present case. (Hcrt =hematocrit).

hematocrit was 18 percent. Transfusion with five units of whole blood raised the hematocrit to 32 percent and the patient was transferred to Stanford University Hospital 36 hours later.

Significant physical findings at that time included mild pallor, tense ascites, and absence of organomegaly or edema. Laboratory studies revealed: Leukocytes 1,300 per cu mm with 78 percent granulocytes and no plasma cells, hematocrit 27 percent, reticulocyte count 2.1 percent and platelet count 57,000 per cu mm. Serum creatinine, serum calcium, BUN and liver function tests were within normal limits. Evidence for a coagulation or hemostatic defect was sought but could not be demonstrated, as evidenced by the following normal studies: PTT, PT, bleeding time (Borchgrevink); thrombin time; clot retraction and plasma euglobulin clot lysis time. Serum protein electrophoresis revealed an albumin of 3.0 gm per 100 ml and a gamma globulin spike of 2.7 gm per 100 ml. There was no proteinuria. Paracentesis yielded non-coagulable sanguinous fluid, studies of which included: hematocrit, 19 percent; leukocytes, 9,000 per cu mm with 95 percent bizarre plasma cells (Figure 1); albumin 2.6 gm and globulin 3.8 gm per 100 ml. Electrophoretic studies of the ascitic fluid were not obtained.

Following transfusion with two units of packed red blood cells, exploratory laparotomy was carried out. Multiple peritoneal nodules and a hemorrhagic 4x4 cm mass adjacent to the right ovary were observed. Splenectomy and a right salpingo-oophorectomy were performed, after which

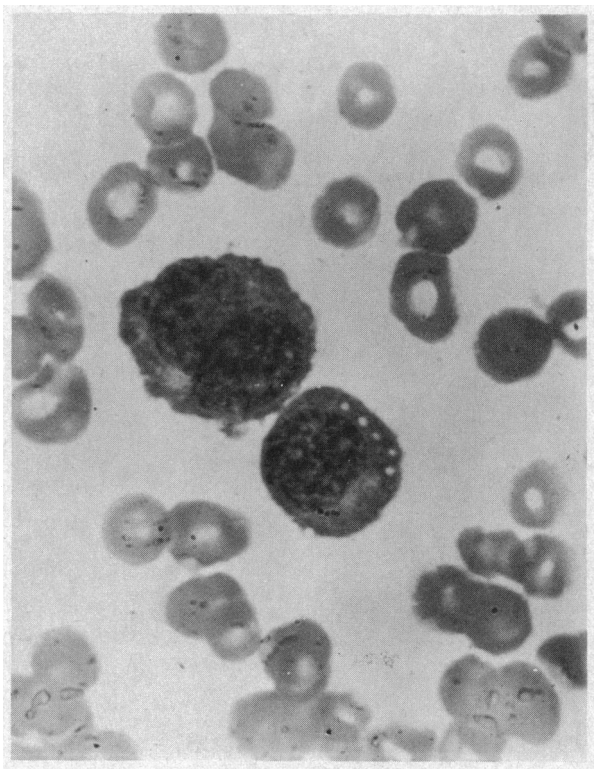

Figure 1.—Representative bizarre plasma cells present in ascitic fluid. (Wright's stain, x 1200).

40 mg of thio-TEPA were instilled into the peritoneal cavity.

The spleen weighed 380 gm and on microscopic examination infiltration of plasma cells was noted. A representative peritoneal nodule (Figure 2) and the right para-ovarian mass proved to be plasmacytomas on microscopic examination. Many of the plasma cells were large and immature.

Following the surgical procedure the patient's course was one of transient improvement, permitting a third course of melphalan-prednisone therapy which was completed 11 March 1970. However, the next day a spontaneous fracture of the right femoral neck occurred which required surgical repair. The ascites gradually reaccumulated and on 21 March 1970 following paracentesis of 3 liters of ascitic fluid, 15 millicuries of radioactive chromic phosphate ($CrP^{32}0_4$) were instilled intraperitoneally. There was no recurrence of ascites, but bilateral lower quadrant masses appeared and progressed to a size of approximately 8x8 cm over a three-week period. Despite a fourth course of melphalan-prednisone, the patient steadily deteriorated, and increasing

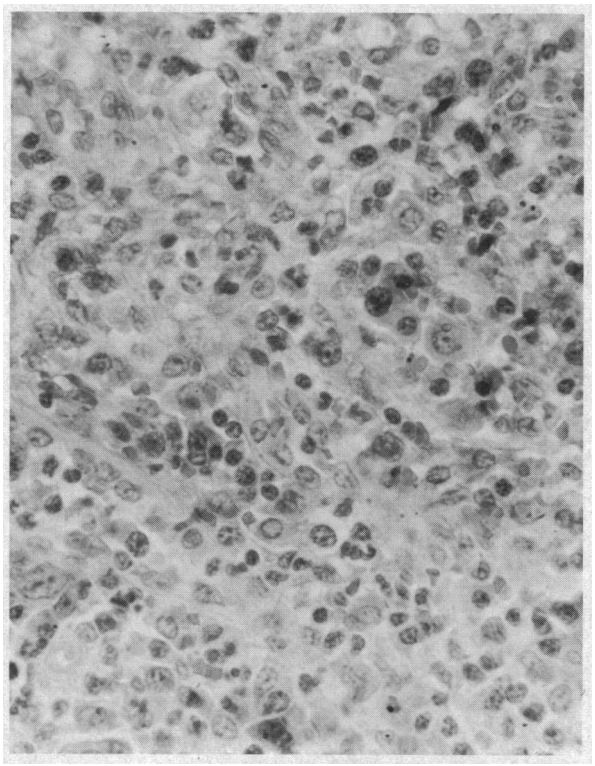

Figure 2.—Section of a representative peritoneal plasmacytoma demonstrating many large, immature plasma cells. (Hematoxylin-eosin, x 320.)

numbers of primitive plasma cells were noted in the peripheral blood. She died 23 April 1970, eight weeks after the onset of ascites, probably from an episode of sepsis. Postmortem examination was not performed.

Comment

Serosal involvement in multiple myeloma is unusual. Pleural[1-4] as well as pericardial[1,3,5] involvement has been sporadically noted in necropsy series of patients with multiple myeloma. Additional case reports have described patients with multiple myeloma and pleural effusions containing large numbers of plasma cells,[6-8] or pleural effusion clearing with cyclophosphamide therapy.[9]

Peritoneal involvement in myeloma is equally rare. Churg and Gordon[1] noted only one such case at autopsy of 30 myeloma patients. Hayes, Bennett and Heck[2] found no peritoneal myeloma involvement in 38 patients and noted only three such instances in a review of the literature. Innes and Newall,[3] and Carson, Ackerman and Maltby,[5] noted no peritoneal involvement in 45 and 27 cases respectively of multiple myeloma at postmortem examination. The rarity of peritoneal involvement contrasts with the more common occurrence of extramedullary myeloma in lymph nodes, liver and spleen.[3]

The appearance of hemorrhagic ascites in the present case is reminiscent of the experimental situation in the BALB/c strain of mice. Multiple peritoneal plasmacytomas and hemorrhagic ascites develop in a high proportion of these mice within 14 months following intraperitoneal injection of mineral oil,[10] or even installation of empty millipore diffusion chambers.[11] Plasmacytoma formation outside the peritoneal cavity is not found. However, hemorrhagic ascites in human myeloma is most unusual. Durant and Barry[9] described a patient with anaplastic multiple myeloma and exudative ascites containing abnormal mononuclear cells, many of which were plasmacytes. The ascites was unresponsive to intracavitary thio-TEPA, but oral cyclophosphamide induced a partial remission. Pruzanski, Platts and Ogryzlo[12] described a patient with plasma cell leukemia in whom ascites developed late in the course of the disease. However, the characteristics of the ascitic fluid were not described in their report and peritoneal implants were not noted at autopsy. An additional patient has been described with plasma cell leukemia and hemorrhagic ascites secondary to spontaneous rupture of an infiltrated spleen.[13]

The appearance of ascites in the present case heralded a rapid deterioration in the clinical course. Intensive therapy with intermittent melphalan-prednisone, as described by Alexanian and coworkers,[14] and intraperitoneal injection of thio-TEPA, did not retard reaccumulation of ascitic fluid. Following the intraperitoneal installation of radioactive chromic phosphate, which has produced a beneficial response in some patients with exudative ascites secondary to lymphoma,[15] ascitic fluid did not reaccumulate. However, the abdominal disease progressed rapidly as manifest by the appearance of bilateral lower quadrant masses.

This case is a further illustration of the protean manifestations of extramedullary myeloma. The diffuse peritoneal disease in this patient supports the contention that anaplastic myeloma may mimic the clinical manifestations of other aggressive disorders of the reticuloendothelial system.[3]

Summary

Hemorrhagic ascites developed 22 months after the diagnosis of multiple myeloma in a woman 45 years of age. The myeloma protein was of the IgG, kappa chain, type. Examination of the ascitic fluid revealed numerous immature plasma cells. Exploratory laparotomy demonstrated multiple peritoneal plasmacytomas. Therapy with melphalan and prednisone, and intraperitoneal instillation of thio-TEPA, did not retard reaccumulation of ascitic fluid. Following injection of radioactive chromic phosphate the ascites did not recur, but bilateral lower quadrant masses developed and the patient died eight weeks after the onset of ascites.

REFERENCES

1. Churg J, Gordon AJ: Multiple myeloma—Lesions of the extraosseous hematopoietic system. Amer J Clin Path 120:934-945, 1950

2. Hayes DW, Bennett WA, Heck FJ: Extramedullary lesions in multiple myeloma. Arch Path 53:262-272, 1952

3. Innes J, Newall J: Myelomatosis. Lancet 1:239-245, 1966

4. Edwards GA, Zawadski ZA: Extraosseous lesions in plasma cell myeloma. Amer J Med 43:194-205, 1967

5. Carson CP, Ackerman LV, Maltby JD: Plasma cell myeloma. Amer J Clin Path 25:849-888, 1965

6. Donnelly WJ, Grahn EP: Extraosseous manifestations of multiple myeloma. Med Cl N Amer 49:229-240, 1965

7. Favis EA, Kerman HD, Schildecker W: Multiple myeloma manifested as a problem in the diagnosis of pulmonary disease. Amer J Med 28:323-327, 1960

8. Abt AB, Deppisch LM: Multiple myeloma involving the extrahepatic biliary system. J Mt Sinai Hosp NY 36:48-54, 1969

9. Durant JR, Barry WE: The changing face of myeloma. Lancet 1:119-121, 1966

10. Potter M, MacCardle RC: Histology of developing plasma cell neoplasia induced by mineral oil in BALB/c mice. J Nat Can Inst 33:497-515, 1964

11. Merwin RM, Algire GH: Induction of plasma-cell neoplasms and fibrosarcomas in mice by diffusion chambers placed in the peritoneal cavity. J Nat Can Inst 31:997-1017, 1963

12. Pruzanski W, Platts ME, Ogryzlo MA: Leukemic form of immunocytic dyscrasia (plasma cell leukemia). Amer J Med 47:60-74, 1969

13. Stephens PJT, Hudson P: Spontaneous rupture of the spleen in plasma cell leukemia. Canad Med Assoc J 100:31-34, 1969

14. Alexanian R, Haut A, Khan AU, et al: Treatment for multiple myeloma—Combination chemotherapy with different melphalan dose regimens. JAMA 208:1680-1684, 1969.

15. Ariel IM, Oropeza R, Pack GT: Intracavitary administration of radioactive isotopes in the control of effusions due to cancer—Results in 267 patients. Cancer 19:1096-1102, 1966

Aseptic Meningitis Following Intrathecal Radioiodinated Serum Albumin

BORINA DRAMOV, M.D., AND
RICHARD DUBOU, M.D., *San Francisco*

THE INTRATHECAL administration of RISA® (radioactive iodinated serum albumin) has been used extensively since 1964 as one means of visualizing the circulation and dynamics of the cerebrospinal fluid (CSF) in normal and pathological conditions. Untoward reactions have been few.[1-5] We are reporting two cases of aseptic meningitis following intrathecal injection of RISA.

Case 1. A 78-year-old right-handed woman had a two-year history of progressive dementia, intermittent fluctuation of consciousness, unsteady gait and urinary incontinence. Neurological examination revealed global dementia, snout, suck and bilateral grasp reflexes, brisk symmetrical muscle stretch reflexes and flexor plantar responses. She had a decidedly unsteady gait. An electroencephalogram revealed diffuse slowing. Because of the possibility of "normal pressure hydrocephalus" and its occasional amelioration by removal of a large volume of CSF[6,7] a lumbar puncture was performed and 40 ml of CSF was withdrawn. The opening pressure was 75 mm of water; the fluid was normal (Table 1). Within a day the patient appeared brighter and incontinence and ataxia disappeared.

Six days later when spinal puncture was done again, 35 ml of CSF was withdrawn and 1.4 ml of 106 μc per ml RISA (10 mg albumin per ml) was injected. Within four hours shaking chills developed and the temperature was 39.8°C. The patient was confused and lethargic and there was pronounced nuchal rigidity. On lumbar puncture 24 hours after the RISA injection, opening pressure was 100 mm. The fluid was cloudy and slightly xanthochromic with pronounced leukocytosis and elevated protein (Table 1). A Gram stain and a culture of the CSF were negative for pathogens. Since the nature of the meningeal reaction was not known, ampicillin and streptomycin were ad-

From the Department of Neurology, Presbyterian Hospital of Pacific Medical Center.

Submitted December 8, 1970.

Reprint requests to: Neurology Department, Presbyterian Hospital of Pacific Medical Center, Clay and Webster Streets, San Francisco, Ca. 94115 (Dr. B. Dramov).